JOINT INVENTORS

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Richard Zimmermann

APPLICATION FOR UNITED STATES LETTERS PATENT

S P E C I F I C A T I O N

TO ALL WHOM IT MAY CONCERN:

Be it known that we, William R. Perrault, a citizen of the United States, residing at 825 Edison Street, in the City of Kalamazoo and State of Michigan and Robert C. Gadwood, a citizen of the United States, residing at 5232 Stonehenge, in the City of Portage and State of Michigan, have invented new and useful METHODS OF PRODUCING OXAZOLIDINONE COMPOUNDS, of which the following is a specification.

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PATENT APPLICATION
28341/6301A.US

METHODS OF PRODUCING OXAZOLIDINONE COMPOUNDS

CROSS-REFERENCE TO RELATED APPLICATION

This application claims the benefit of provisional patent application Serial No. 60/241,122, filed October 17, 2000.

FIELD OF THE INVENTION

The present invention relates to a method of preparing pharmacologically active oxazolidinones and various intermediates used in the method. The oxazolidinone derivatives are useful as broad spectrum antimicrobial agents which are effective against a variety of human and veterinary pathogens.

BACKGROUND OF THE INVENTION

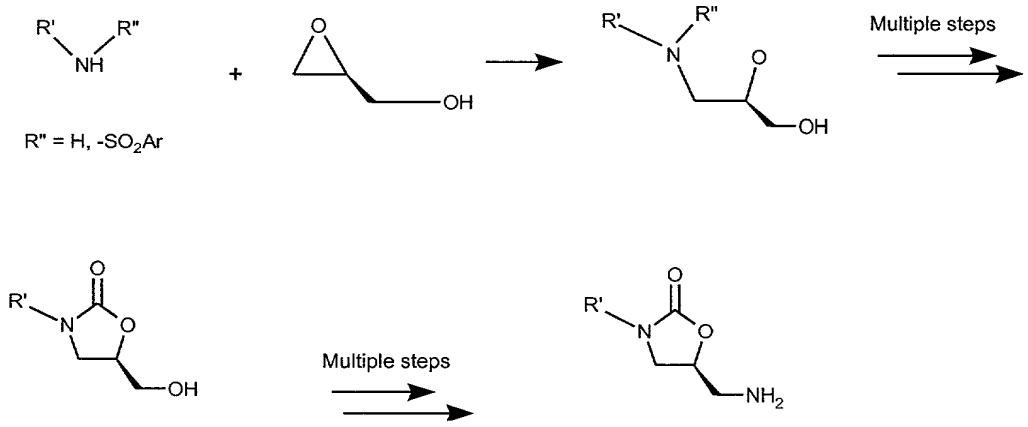
Compounds that contain the 5-acetamidomethyl-oxazolidinone moiety are well known to persons skilled in the art as pharmacologically useful antibacterial agents. For example, U.S. Patents 5,164,510, 5,182,403, and 5,225,565 disclose antibacterial 5'-indolinyl-oxazolidinones, 3-(5'-indazolyl)-oxazolidinones, and 3-(fused-ring substituted)phenyl-oxazolidinones, respectively. Similarly, U.S. Patent Nos. 5,231,188 and 5,247,090 disclose several tricyclic [6.5.5] and [6.6.5]-fused ring - oxazolidinones which are useful pharmaceutical agents. International Publication WO93/09103 discloses antibacterial mono- and di-halophenyl-oxazolidinones.

Persons skilled in the art use two primary methods to prepare the 5-acetamidomethyl-oxazolidinone moiety of these therapeutic agents. The first method involves condensation of an aromatic carbamate (Ar-HN-C(=O)-OR) or aromatic isocyanate (Ar-N=C=O) with a halopropanediol or another nitrogen-free three-carbon reagent to provide an intermediate oxazolidinone having a hydroxymethyl substituent at the C-5 position of the oxazolidinone. The hydroxyl group then is replaced by an

acetamido group to give a pharmacologically active 5-acetamidomethyl-oxazolidinone.

Many variants of this two-step process have been developed, and examples are illustrated in U.S. Patent Nos. 4,150,029, 4,250,318, 4,476,136, and 4,340,606, which disclose the synthesis of 5-hydroxymethyl-oxazolidinones from amines (Scheme A). The mixture of enantiomers produced by this process are

Scheme A



separated by fractional crystallization of their mandelic acid salts. The enantiomerically pure R-diol then is converted into the corresponding 5-(R)-hydroxymethyl-oxazolidinone by condensation with diethylcarbonate in the presence of sodium methoxide. The 5-(R)-hydroxymethyl-oxazolidinone then is aminated, and the resulting amine acylated in subsequent steps.

Likewise, U.S. Patent No. 4,948,801, *J. Med. Chem.*, *32*, 1673 (1989), and *Tetrahedron, 45*, 1323 (1989) disclose a method of producing oxazolidinones which comprises reacting an isocyanate (R-N=C=O) with (R)-glycidyl butyrate in the presence of a catalytic amount of a lithium bromide-tributylphosphine oxide complex at 135-145°C to produce the corresponding 5-(R)-butyryloxymethyl-oxazolidinone. The butyrate ester then is hydrolyzed in a subsequent step to provide the corresponding 5-(R)-hydroxymethyl-oxazolidinone. The 5-(R)-hydroxymethyl-oxazolidinone then is aminated in a subsequent step.